Refer to: Gittes RF, Bendixen HH: Pheochromocytoma—Tumor localization and surgical management. Calif Med 118: 1-6, June 1973

California Medicine
THE WESTERN JOURNAL OF MEDICINE

Pheochromocytoma

Tumor Localization and Surgical Management

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Recent experience with five cases of pheochromocytoma is the basis for this report. Pharmacological blockade is to be started with phenoxybenzamine before angiographic studies. Arteriography is the preferred localization technique, particularly when combined with bone-subtraction films.

Anesthetic management requires special attention to premedication, close monitoring of cardiac rhythm, arterial and central venous pressure, and judicious administration of alpha and beta blockers. Methoxyflurane is no longer the anesthetic agent of choice because of possible nephrotoxicity.

Multiple tumors are common. Wide surgical exposure with systematic palpation of autonomic ganglia must be carried out. Manipulation of the tumor does raise arterial blood pressure in spite of adequate preoperative blockade. The alpha blockade prevents the sudden and dangerous vascular collapse which used to be seen after removal of the tumor.

RECENT EXPERIENCE with five cases of pheochromocytoma forms the basis for the present review of the clinical management of this dramatic disease. For safe, successful therapy, particular emphasis needs to be placed on (1) optimal pharmacological treatment to see the patient safely through diagnostic angiography and surgical anesthesia, and (2), the use of refined radiological techniques with thorough surgical exploration to detect multiple and extra-adrenal tumors.

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Submitted January 8, 1973.

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Case Summaries

CASE 1. A 41-year-old man diagnosed himself as having pheochromocytoma "again" because of a recurrence of severe headaches and perspiration eight years after the surgical removal of his left adrenal gland for a benign pheochromocytoma. Episodic hypertension was noted and catecholamine derivatives in the urine were elevated. An excretory urogram was normal.

Phenoxybenzamine (Dibenzyline®) was prescribed, 50 mg twice a day. After five days he was asymptomatic and normotensive, his hematocrit had dropped from 44 to 36 percent and angiography was deemed safe. Abdominal aortography

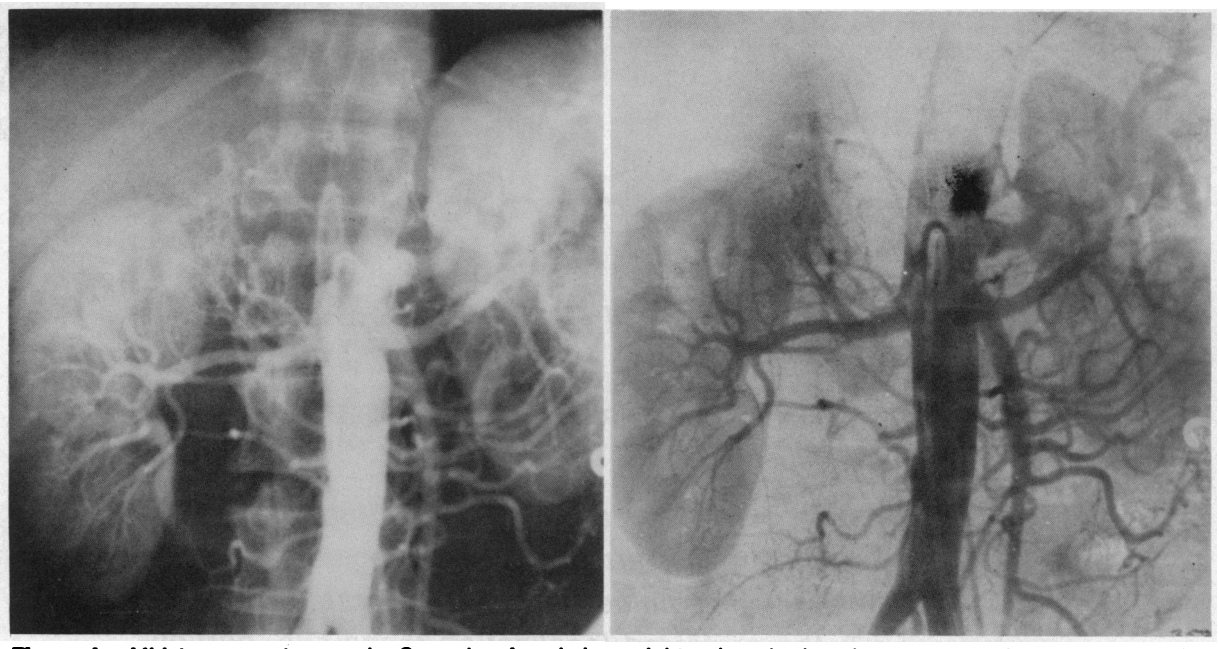

Figure 1.—Midstream aortogram in Case 1. An obvious right adrenal pheochromocytoma is seen on routine films (left). By use of the bone-subtraction technique (right), the round second tumor is seen overlying the third lumbar vertebra behind the vena cava.

as well as selective angiography at first revealed only the obvious pheochromocytoma in the right adrenal gland (Figure 1).

Phenoxybenzamine was continued for four more days, and surgical exploration then was carried out. The day before operation the patient received propranolol, 10 mg four times a day. Anesthesia was induced with thiopental sodium after premedication with 150 mg of pentobarbital and was maintained with methoxyflurane 0.3 to 1.0 percent, for a total duration of 160 minutes. Exploration included careful palpation of all autonomic ganglia along the aorta and cava. Behind the cava, at the level of the renal veins, a second tumor was palpated and dissected out. It was separate from the larger, encapsulated and benign-appearing tumor in the right adrenal gland. Histology suggested two benign pheochromocytomas, the smaller presumably arising in a sympathetic ganglion.

A review of the angiograms with the use of photographic bone-subtracting technique (Figure 1) clearly outlined the tumor blush of the second tumor, overlying the paravertebral tissue. At last report the patient was normotensive on corticoid replacement therapy.

CASE 2. A 21-year-old woman with von Recklinghausen's neurofibromatosis was studied because of a consistent, non-episodic hypertension. Due to the high incidence of pheochromocytoma in patients with neurofibromatosis, determinations of urinary catecholamines and derivatives were ordered and the values were found to be elevated.

Administration of phenoxybenzamine, 10 mg every six hours, was begun. After four days the dose was increased to 20 mg every six hours. The blood pressure remained variable and averaged approximately 165/100 mm of mercury during the preoperative period.

On the third hospital day, aortography revealed a large vascular tumor in the left adrenal gland. During angiography and immediately afterward the patient complained of abdominal pain and the blood pressure rose to 200/140 mm. Phentolamine (Regitine®) was infused intravenously, and oral dibenzyline was increased to a dose of 20 mg every six hours. Operation was postponed. By the ninth day the blood pressure was relatively stable around 160/100 mm and the hematocrit had dropped from 44 to 34 percent. The patient was taken to surgery.

After premedication with Innovar®,* diphenhydramine and atropine and under thiopental sodium, curare and methoxyflurane anesthesia, the large principal tumor was removed. But, in addition, the transabdominal exploration revealed edematous enlargement of the coeliac ganglion and when it was removed and bisected a small tumor was found in the center. The blood pressure during surgical manipulation of the tumors rose as high

*A combination of fentanyl and droperidol.

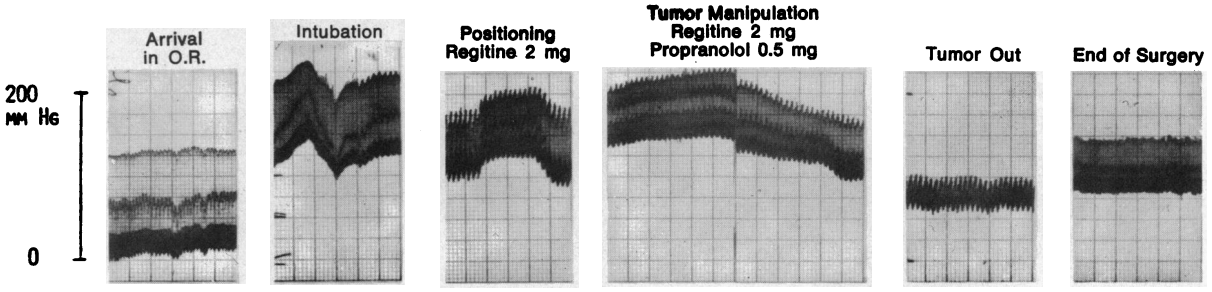

Figure 2.—Actual tracings of intra-arterial pressure monitor during course of anesthesia in Case 2. In spite of extensive preoperative blockade with phenoxybenzamine, hypertensive attacks are recorded during intubation, positioning, and tumor manipulation.

as 230/140 mm (Figure 2), requiring intermittent use of phentolamine and propranolol, in doses of 2 and 0.5 mg respectively. After the operation the blood pressure remained within normal limits.

CASE 3. A 43-year-old man with severe hypertension had positive chemical findings for pheochromocytoma. After five days on phenoxybenzamine, 20 mg every six hours, and propranolol, 10 mg every six hours, the blood pressure was variable, ranging from 200/100 to 150/80 mm of mercury, and there was a drop of only 3 percent (37 to 34 percent) in the hematocrit. The phenoxybenzamine was increased to 20 mg every four hours. Midstream aortography outlined not only a large right adrenal pheochromocytoma, but also a definite irregularity in the wall of the main right renal artery, with occlusion of several branches of the upper pole of the kidney (Figure 3). By the ninth day the hematocrit was still 34 percent, but blood pressure and pulse were stable. Surgical exploration was done under methoxyflurane anesthesia after premedication with morphine, hydroxyzine and thiopental sodium. The kidney was found mottled with large yellow areas of infarction. The tumor and kidney were resected *en bloc*. No other tumor was found.

On pathological examination a well encapsulated pheochromocytoma was found in association with an organized dissecting aneurysm of the renal artery, with occlusion of several distal branches and segmental renal infarction.

During the procedure the blood pressure ranged

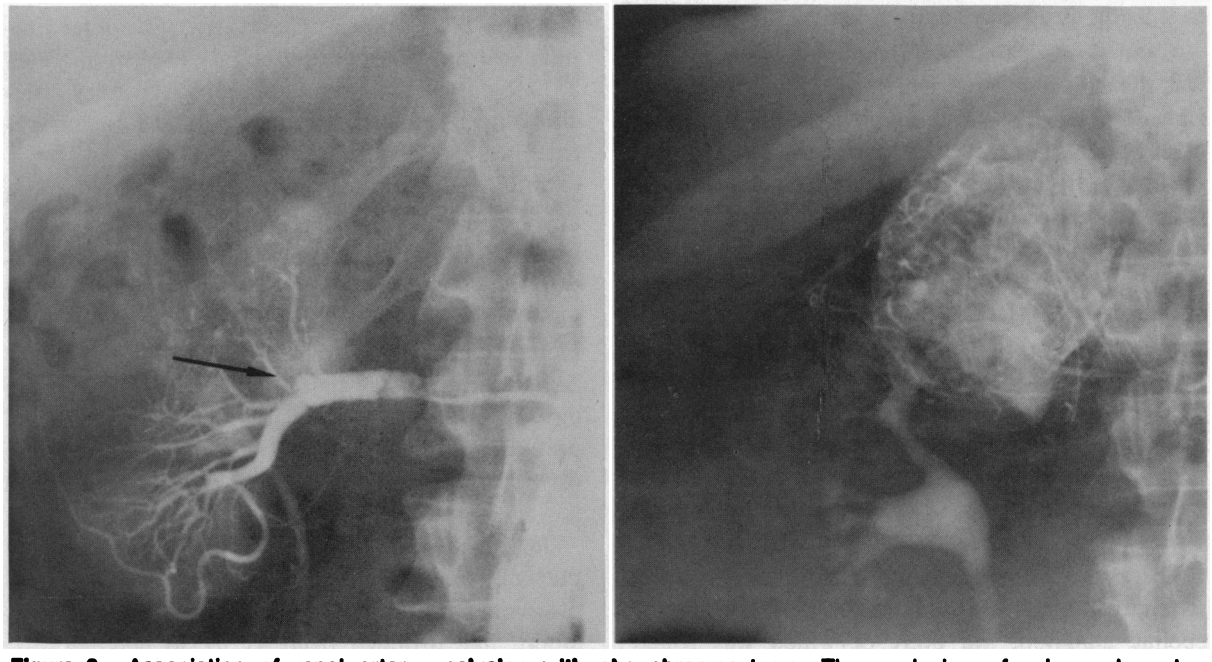

Figure 3.—Association of renal artery occlusion with pheochromocytoma. The occlusion of primary branches (arrow) was noted on the preliminary midstream aortogram and was due to an established spontaneous dissecting aneurysm of the main renal artery. The large pheochromocytoma is shown in detail in a selective angiogram of the right middle adrenal artery.

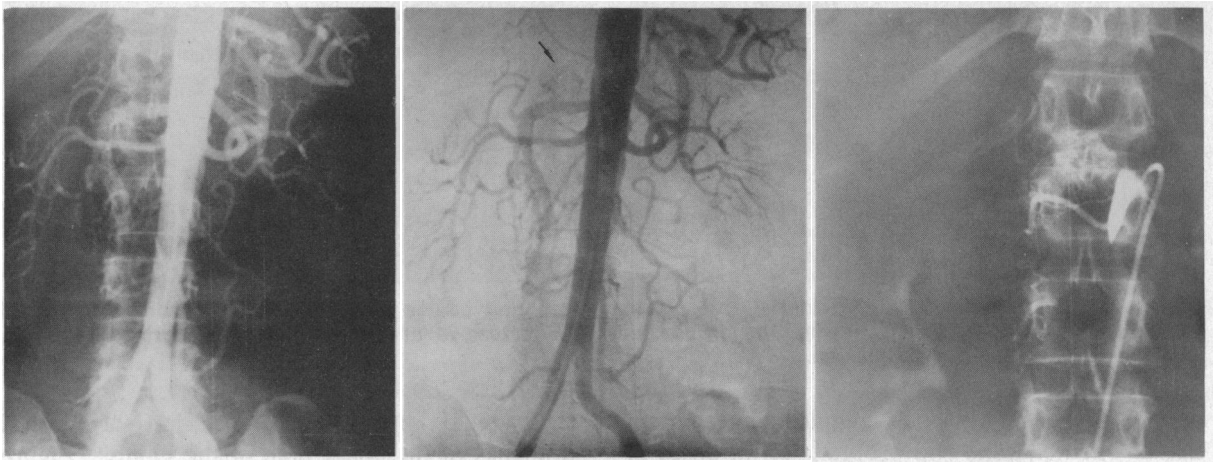

Figure 4.—Angiography with bone-subtraction demonstrates a pheochromocytoma of the right coeliac ganglion. The tumor masked by the first lumbar vertebra in the standard film (left) is only seen after the immediately performed bone subtraction (center, arrow) and is then further defined by the selective arteriogram of the lumbar artery (right).

between 230/130 and 70/40 mm of mercury. The duration of anesthesia was 4.20 hours, with methoxyflurane concentrations ranging from 0.2 to 1.5 percent.

Postoperatively the patient had evidence suggestive of high output renal failure, with 24-hour urine volumes between 1,200 and 4,650 ml and serum creatinine climbing to a maximum of 5.4 mg on day five. Urine oxalate on the eighth postoperative day was normal. The patient remained normotensive and the creatinine slowly decreased to 2.9 mg at 14 days and to 1.3 by the 38th day.

CASE 4. Continuous significant hypertension was the only symptom which prompted the physician of a 50-year-old woman to perform a diagnostic phentolamine (Regitine®) test—and it was positive. Urine tests confirmed the diagnosis of pheochromocytoma. After 12 days on phenoxybenzamine, 40 to 60 mg per day, the hematocrit dropped from 46 to 43 percent and the blood pressure ranged from 180/100 to 145/80 mm of mercury. Then angiography was done, and no tumor blush was seen in the routine films (Figure 4). But immediate bone-subtraction films (Figure 4 *center*) did show a 2 cm tumor overlying the body of the first lumbar vertebra; then selective angiography (Figure 4 *right*) outlined the tumor in the area of the coeliac ganglion.

Exploration one day later, after continued alpha adrenergic blockade, led to the removal of the coeliac ganglion, the body of which was found to be supplanted by a typical pheochromocytoma. No other tumors were found.

Anesthesia was induced with thiopental sodium and maintained with nitrous oxide, meperidine and curare. During the procedure phentolamine, 5 mg, was needed intermittently to control the blood pressure. After the operation the blood pressure remained within normal range.

CASE 5. A 39-year-old woman was treated for hypertension accompanied by severe epistaxis, headaches, increased nervousness, tachycardia, palpitations and syncope. The blood pressure had recently been measured at 260/160 mm of mercury. The patient was transferred to University Hospital of San Diego County from another hospital one day after aortography had demonstrated a 6x9 cm right suprarenal mass. Urinary catecholamines, vanillylmandelic acid and metanephrines were decidedly elevated.

The patient's blood pressure was 240/140 mm at the time of admission, and a phentolamine infusion was used for immediate control. Administration of phenoxybenzamine, 10 mg every six hours was begun. Four days later the dose was increased to 20 mg every six hours; after another day to 30 mg every six hours; and after two more days to 40 mg every six hours. The total period of pretreatment was 14 days, during the last seven of which the patient also received propranolol, 10 mg every six hours.

It was not until the last two days preoperatively that the blood pressure was fairly stable at approximately 170/105 mm of mercury. The hematocrit had dropped from 41 to 36 percent.

Two weeks following admission the patient was premedicated with morphine and hydroxyzine; anesthesia was induced with thiopental sodium

and maintained with N_2O, curare and methoxyflurane. Resection of the pheochromocytoma was carried out. No other tumors were found. The blood pressure remained well controlled throughout, in the range of 160/90 to 120/70 mm. No phentolamine or propranolol was needed. The postoperative course was without circulatory problems and the blood pressure was within normal range thereafter.

Pharmacological Management

Recent advances in the use of adrenergic blockers make possible the prevention of some, but not all, of the dramatic swings in blood pressure during surgical treatment of pheochromocytoma.[1-5] Certainly eliminated by adequate preangiographic and preoperative adrenergic block is the lability of blood pressure under minor stress. Also eliminated is the occurrence of the profound hypotension that otherwise ordinarily follows removal of the tumor. Most fatalities from pheochromocytoma in the past were associated with the late and profound hypotension, not with the earlier hypertensive crises.[6]

The principal effect of pretreatment with alpha adrenergic blocking drugs such as phenoxybenzamine may well be the elimination of sustained vasoconstriction and the restoration of normal volume of circulating blood. A fall in hematocrit in the absence of blood loss to explain it, warns of the expansion of the contracted vascular bed in time to avoid sudden vascular collapse at the time of removal of the tumor. Elective transfusion may be required preoperatively if the hematocrit drops below 35 percent.

Pretreatment with adrenergic blocking drugs also lowers the blood pressure and gives the patient symptomatic relief from headache, palpitations, nausea, anxiety and sweating. Phenoxybenzamine is the preferred agent, as it is long-acting and is given by mouth. Commonly, too small doses are used. The effective dose is 1.0 to 2.0 mg per kg of body weight per 24 hours, divided into three or four doses. Side effects are the characteristic nasal congestion and orthostatic hypotension. When phenoxybenzamine treatment is started, the patient should be confined to bed until normal blood pressures are achieved along with a drop in hematocrit of about 5 percent. Fear of orthostatic hypotension must not lead to undertreatment.

Pretreatment also with beta adrenergic blocking agents, such as propranolol, has been advocated. Because of the relatively short action of these drugs, they cannot sustain protection, nor are they strongly indicated except in the face of persistent arrhythmias or sinus tachycardia exceeding 120 beats per minute. Methyl tyrosine, an inhibitor of the enzyme tyrosine hydroxylase, has been advocated for chronic management of pheochromocytoma,[1] but it can be toxic.[4] We have not used it. The majority of patients are adequately pretreated with phenoxybenzamine alone.

Premedication before operation is of special importance to reduce anxiety and the accompanying high blood pressure. The premedication of choice is pentobarbital sodium, which will obtund cortical arousal and reticular activation.

For the same reasons, thiopental sodium is the induction agent of choice. Succinylcholine is used for intubation after a small dose of curare to avoid fasciculations. Much has been written about the choice of agents for maintenance of anesthesia.[1,2,4] There is general agreement that cyclopropane should be avoided; but diethyl ether, halothane, methoxyflurane and N_2O-relaxant-narcotic combinations have been used successfully. Methoxyflurane enjoyed special favor for a time, but in our opinion the potential nephrotoxicity has recently taken it out of contention.[14] We used methoxyflurane in four of our five cases. In one of the cases herein reported (Case 3) the combination of oliguria in the immediate postoperative period followed by high urine outputs associated with rising values of serum creatinine could have represented the high-output renal failure associated with this anesthetic.

During operation, indwelling catheters permit continuous recordings of arterial and central venous pressures. In addition, the electrocardiogram is displayed on an oscilloscope and the body temperature is measured. Such close monitoring provides precise data for patient management and gives early warning of any deleterious trend. All patients receive controlled ventilation, guided by the arterial blood gas measurements.

Despite adequate pretreatment, hypertensive episodes may be expected when the patient is moved, or on endotracheal intubation, or while the abdomen is being prepared; and especially such episodes are associated with retraction or manipulation of the tumor. The short-acting alpha-blocking agent, phentolamine, is used in intermittent doses of 1 to 5 mg to blunt the hypertensive peaks. Persistent arrhythmia or tachycardia is treated with propranolol in intermittent doses of

0.5 to 1.0 mg. While norepinephrine is kept in readiness, the first treatment of the falling blood pressure after tumor removal should be volume replacement. Only rarely should norepinephrine be required at this time, provided adequate blood volume has been maintained.

Radiological and Surgical Exploration

We have learned to depend heavily on preoperative angiographic localization[7] rather than plasma catecholamine levels[8] or surgical exploration alone.[4] Aortography and selective angiography must be undertaken only after adrenergic blockade is established, and even then intravenous phentolamine and propanolol must be at hand and the pressure and pulse closely monitored.

Immediate bone-subtraction films should be processed after the initial midstream aortogram. Two of the patients here reported upon had tumors seen only with this technique (Figures 1 and 4). A suspicious blush is then defined further by selective angiography, as in the coeliac ganglion tumor in Case 4. Multiple tumors may be anticipated in 15 percent of adults,[4] and therefore the angiograms must be scrutinized for a second tumor even when an obvious tumor is seen. Multiplicity or bilaterality is particularly common in patients with familial neuroectodermal disease such as neurofibromatosis[9] or familial pheochromocytoma associated with medullary carcinoma of the thyroid.[10]

Close attention to the kidney vessels on the angiograms is suggested by the association of renal artery stenosis and pheochromocytoma,[11] illustrated in Case 3. The size of the tumor is often such that it involves the branches of the renal artery, and part or all of the kidney may be sacrificed.[12] For these reasons, the surgeons must have familiarity with renal surgery, and the condition of the opposite kidney must be determined beforehand.

Meticulous and systematic transabdominal exploration is still required in spite of the angiographic advances such as bone-subtraction films and selected angiograms. Careful palpation of the vena cava, coeliac and hypogastric plexus, and both sympathetic chains may reveal an unsuspected second tumor, as in Cases 1 and 2 herein. When a large tumor is present (Cases 2, 3, 5) a thoraco-abdominal incision is preferred for optimal exposure and vascular control of the adrenal area.

Postoperatively the monitoring with intra-arterial and central venous catheters is to be maintained at least 24 hours. The well-managed patient with adequate vascular volume will not have hypotension unless it is cardiogenic.[4,13] Postoperative hypertension might suggest residual tumor or renovascular damage,[12] and these possibilities are sorted out by repeated determinations of urinary catecholamines and plasma renin values, and by further arteriography if necessary.

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